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REVIEW ARTICLE

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The effect of mouthrinses on oral malodor: a systematic review

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Abstract: *Objective*: The objective of this study is to systematically review the literature regarding the impact of mouthrinses on oral malodor and present evidence for the treatment effects of mouthrinses on oral malodor. *Material and methods:* PubMed-MEDLINE, the Cochrane-CENTRAL and EMBASE were searched through February 10, 2012 to identify appropriate studies. Volatile sulphur compound measurements, organoleptic measurements and tongue coating were selected as outcome variables. *Search results*: The independent screenings of 333 unique titles and paper abstracts revealed 12 publications (12 experiments) that met the eligibility criteria. Means and standard deviations were extracted. The results were separated into short-term (<3 weeks) and longer-term (≥3 weeks) studies. *Conclusion*: In this review, nearly all mouthwashes with active ingredients had beneficial effects in reducing oral malodor in both short- and longer-term studies. The most compelling evidence was provided for chlorhexidine mouthwashes, and those that contained a combination of cetyl pyridinum chloride and zinc provided the best evidence profile on oral malodor. Little data with respect to tongue coating were available, and none of the studies showed a beneficial effect for this parameter.

Key words: bad breath; mouthrinses; mouthwashes; oral halitosis; oral malodor; organoleptic measurements; systematic review; tongue coating; volatile sulphur compounds

Introduction

Oral malodor, or bad breath, is a general term that is used to describe an offensive odour emanating from the oral cavity. This condition is caused by several factors (1–3). Representative epidemiological reports have shown that approximately 87% (4) to 86% (5) of bad breath cases have an oral cause. Although some extra-oral causes (e.g. nasal inflammation, diabetes mellitus and uraemia) have been suggested, clinical studies have shown that gingivitis, periodontitis and tongue coatings are the primary sources (2, 6, 7). The reliability of epidemiological data has been questioned; however, the prevalence of halitosis has been reported to be as high as 50% (8, 9). Of all halitosis cases, only approximately 5–8% can be attributed to non-oral causes (5, 10).

Volatile sulphur compounds (VSCs) are the major components of malodor that originate from the oral environment. Specifically, hydrogen sulphide (H_2S), methyl mercaptan (CH_3SH) and dimethyl sulphide [$(CH_3)_2S$] are the major VSCs that are involved in oral malodor. The substrates for VSCs are sulphur-containing amino acids (i.e. cysteine, cystine and methionine) that are found in saliva, gingival cervical fluid

and tongue-coating debris (2, 11). The chief VSC components are hydrogen sulphide and methyl mercaptans (1, 12). Volatile sulphur compounds, in addition to other malodorous compounds, such as indole, skatole, putrescine and cadaverine (13), are produced through the bacterial metabolic degradation of food debris, desquamated cells, saliva proteins, dental plaque and microbial putrefaction (14). The periodontal pocket also provides an ideal environment for VSC production, which explains why patients with periodontal disease often complain of oral malodor (15). The bacteria that are associated with gingivitis and/or periodontitis, such as *Porphyromonas gingivalis* (16) and *Prevotella intermedia* (17), are known to produce large amounts of these VSCs. Tongue coatings (TCs) can also provoke bad breath (6, 11, 18–22). Indeed, the fissures and crypts of the tongue harbour large amounts of the aforementioned bacterial species (18, 21).

The success of any oral malodor intervention appears to hinge on the reduction in VSC levels and other foul volatiles. Consequently, the majority of oral malodor products focus on mechanical and chemical options. Mechanical interventions (i.e. brushing, flossing and tongue scraping) aim to reduce the numbers of VSC-producing bacteria, residual food matter and cellular debris from the gingiva and tongue. In moderate periodontitis patients, initial periodontal therapy can be expected to improve breath odour parameters (18).

In a recent systematic review concerning the effectiveness of tongue cleaning, various parameters for oral malodor were evaluated. Mechanical approaches, such as tongue brushing, tongue scraping, and cleaning of the dorsum of the tongue, have the potential to successfully reduce oral malodor. However, data concerning the effect of mechanical tongue cleaning on chronic oral malodor are insufficient (23). The limitations of mechanical methods to effectively remove or reduce VSC-producing bacteria from all oral ecological sites are acknowledged. It is possible that mouthrinses may be more effective or at least adjunctively effective in reaching the less accessible parts of the oral cavity. The greater social acceptance and ease of use of mouthrinses have led to the development of a large number and range of over-the-counter products (24, 25). A number of mouthrinses contain antibacterial agents in addition to flavouring agents and have been generally categorized into groups that neutralize odour and groups that mask odour. Components that neutralize odour can further be divided into those that directly affect bacteria and those that neutralize the chemical compounds that the bacteria produce. These include chlorhexidine, phenol, triclosan, chlorine dioxide, alcohol and metal ions, of which the most common metal ion is zinc (26, 27). These components have been tested alone, in combination, and together with mechanical devices for their efficacy to reduce oral malodor (2, 28).

The Cochrane collaboration recently published a systematic review concerning mouthwashes and their effect against oral malodor (9). This review included papers that not only had a control group but also compared mouthwashes with different active ingredients. Additionally, papers that were included in the review used eligibility criteria that included a requirement of a minimum follow-up period of 1 week. Because of the latter inclusion criterion, the number of included studies decreased to five. The small number of included studies limited the extent to which that review could be generalized. Hence, the aim of the present comprehensive review was to investigate the effect of mouthrinses on oral malodor in comparison with placebo/control mouthwash in studies with patients who used the mouthwash multiple times for a minimum follow-up period of more than 1 day.

The current review followed the recommendations that were outlined in the guidelines for transparent and complete reporting of systematic reviews and meta-analysis (29, 30).

Materials and methods

Search strategy

Three Internet sources were used to search for appropriate papers satisfying the study purpose: The National Library of Medicine, Washington, D.C. (PubMed-MEDLINE), The Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE (Excerpta Medical Database by Elsevier). All of the databases were searched for studies from their earliest records until February 10, 2012. The search was designed to include any published study that evaluated the effect of a mouthwash on oral malodor (Box 1).

Screening and selection

Papers were independently screened by two review authors (GAW & TB). Each paper was reviewed first by title and abstract. Only papers that were written in English were accepted. Case reports, letters, and narrative or historical reviews were not included. If the search keywords were present in the title of a paper, the abstract was read. Suitable abstracts were selected, and a full reading of the paper was performed. If

Box 1. **The search strategy that was developed for PubMed-MEDLINE and then customized for the COCHRANE-CENTRAL and EMBASE databases**

The asterisk (*) was used as a truncation symbol, and the limits 'English' and 'Human' were used

The following terms were used in the search strategy:
<(intervention) AND (outcome)>

<(**Intervention:** [MeSH terms/all subheadings] Mouthwashes OR [text words] Mouthwashes OR Mouthwash OR mouthwash* OR mouthrinses OR mouthrinse)

AND

(**Outcome:** [MeSH terms/all subheadings] Carbon Disulfide OR Acetone OR Hydrogen Sulfide OR Halitosis OR [Substance Name] dimethyl sulfide OR dimethylamine OR trimethylamine OR [text words] halitosis OR oral malodor OR halimetry OR bad breath OR morning breath odor OR volatile sulfur compounds OR Volatile sulphur compounds OR methyl mercaptan OR hydrogen sulfide OR tongue coating OR methyl propyl sulfide OR allyl methyl sulfide OR carbon disulfide OR acetone OR trimethylamine OR dimethylamine OR dimethyl sulfide OR foetor ex ore OR breath)>

an abstract was not present, the paper was also selected for full-text reading so that the paper could be screened for eligibility. After selection, two reviewers (DES & TB) read the full-text papers in detail. Papers that fulfilled all of the selection criteria were processed for data extraction. Two reviewers (DES & TB) hand-searched the reference lists of all of the included studies for additional papers that met the eligibility criteria for this review.

Unpublished data were not assessed. Disagreements were resolved by discussion, and if a disagreement persisted, the judgment of a third reviewer (GAW) was decisive.

The eligibility criteria were as follows:

- Randomized controlled trials (RCTs) or controlled clinical trials (CCTs).
- Studies conducted in people ≥18 years old and in good general health.
- Intervention: mouthwash with an active ingredient.
- Comparison: placebo/control mouthwash (without active ingredients).
- Evaluation parameters: VSCs, organoleptic measurement (OM), tongue coating (TC).
- Multiple uses of the mouthwash.
- Study duration: greater than 1 day.
- No mechanical tongue cleaning was performed.

Assessment of heterogeneity

The heterogeneity of the primary outcome across studies was detailed according to the following factors:

- Study design and evaluation period.
- Characteristics of the participants.
- Characteristics of the intervention and hygiene instructions.
- Industry funding.

Quality assessment

Two reviewers (TB & DES) scored the methodological quality of the included studies. Again, any disagreement between the two reviewers was resolved after additional discussion. If a disagreement persisted, the judgment of a third reviewer (GAW) was decisive. The quality of the study methodology was assessed as proposed by the RCT checklist of the Dutch Cochrane Center (2009). This assessment was completed with quality criteria that were obtained from the CONSORT statement (2010) (31, 32), the Jadad scale (33) and the Delphi List (34). The criteria were chosen to assess the following domains: internal validity, external validity and statistical methods (35).

Studies with random allocation, defined inclusion and exclusion criteria; blinding to the patient and examiner; balanced experimental groups; identical treatments among groups except for the intervention; reports of follow-up and point estimates were classified as having a low risk of bias. Studies that failed to satisfy one of these eight criteria were classified as having a moderate risk of bias. When two or more of the criteria were not satisfied, studies were considered to have a high risk of bias. These criteria comply with the Cochrane handbook assessment of potential 'risk of bias', and 'allocation concealment' was not included as a criterion in this assessment, as proposed by Van der Weijden *et al.* (36). Importantly, studies that qualified for the review on the basis of the inclusion criteria were not excluded because of their quality assessment classifications.

Data extraction and analysis

In accordance with the Acceptance Program Guidelines (37–39) that have been established by The American Dental Association (ADA), the reviewed studies were separated into short-term and longer-term study period groups (longer-term studies lasting ≥3 weeks). A summary table was then constructed using the collected information (Appendix S3a–c). Data concerning the effectiveness of mouthrinses in comparison with a placebo/control against oral malodor, as measured by VSC contents, OMs, and TC, were collected from papers that satisfied the inclusion criteria. Mean values and standard deviations (SDs) were extracted for baseline, end-trial and incremental time points for the parameters of interest (DES & TB). Some of the studies provided standard errors (SE) of the mean. If possible, the authors calculated for these studies the standard deviations based on the sample size ($SE = SD/\sqrt{N}$). The provided data were analysed in a descriptive format (Table 2) for short-term and longer-term studies. Data from the selected studies did not allow for a meta-analysis owing to heterogeneity in the study designs, products used, outcome measures and data presentation.

Evidence profile

The Grading of Recommendations Assessment, Development and Evaluation (GRADE) system that has been proposed by the GRADE working group was used to classify the body of evidence that emerged from this review (40). Two reviewers (DES & GAW) rated the quality of the evidence for outcome across the studies. Any disagreement between the two reviewers was resolved after additional discussion.

Results

Search and selection

The PubMed-MEDLINE search resulted in 259 citations, the EMBASE search in 86 citations and the Cochrane-CENTRAL search in 78 citations (for details, see Fig. 1). While papers were identical in the searches, a total of 333 unique papers were found. The title and abstract screening initially resulted in 41 full-text articles. In total, 29 papers were excluded for failing the eligibility criteria, and the studies that were rejected at this stage were recorded in a rejection table along with the reasons for rejection (see Appendix S1). No additional articles were detected after searching the references of the selected full-text papers. In total, 12 papers were identified to be eligible for inclusion into this review according to

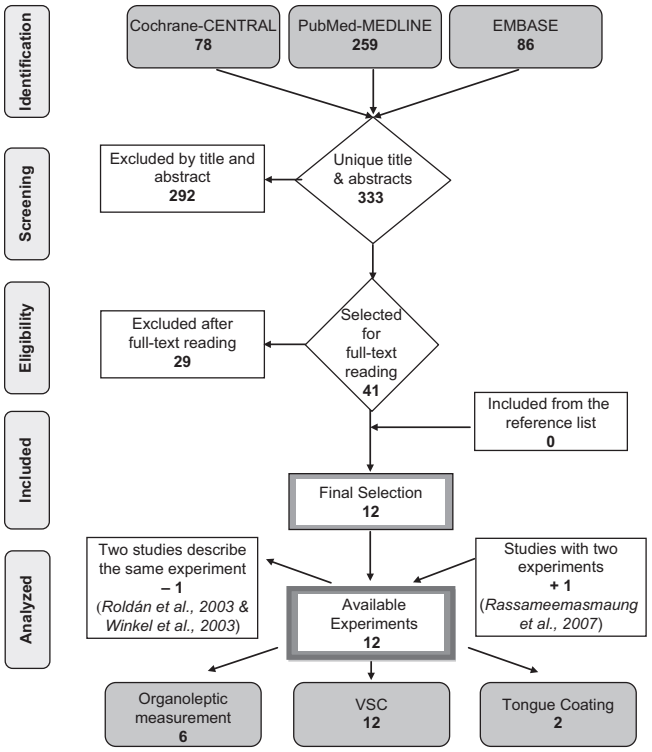

Fig. 1. The search and selection results.

the defined criteria for the study design, participants, intervention and outcome. It is notable that the same experiment was presented in two separate papers: Roldán *et al.* (28) and Winkel *et al.* (41). Additionally, Rassameemasmaung *et al.* (42) presented two separate experiments (with and without oral prophylaxes). Therefore, a total of 12 experiments were processed for data extraction.

Assessment of the study heterogeneity

Considerable heterogeneity was observed in the interventions, regimens, concentrations of products used and outcome variables. Furthermore, the number, gender and age of participants varied among the studies. Information regarding the study outline characteristics is shown in Table 1a for short-term studies and Table 1b for longer-term studies.

Study design and evaluation period

Each of the 12 included experiments had an RCT design. In total, six of these experiments had a crossover design (I, II, IV, V, VI and VIII) and six had a parallel design (III a+b, VII, IX, X and XI). The articles were divided into short-term (<3 weeks) and longer-term (≥3 weeks) studies. The short-term evaluation period varied from 4 days (II and V) to 2 weeks (III and VII). For the longer-term studies, the shortest evaluation period was 3 weeks (IX) and the longest evaluation period was 4 weeks (X and XI). Four experiments (II, V, VI and VIII) used a non-brushing model.

Five of the experiments (II, IIIb, V, VI and VIII) implemented oral prophylaxes as part of the study protocol, whereas seven (I, IIIa, IV, VII, X, XI and IX) did not use oral prophylaxes prior to the experiment. Study III a+b described two experiments, and these experiments specifically compared the effect of oral prophylaxes on the experimental intervention and control groups.

Characteristics of the participants

- *Medical status/smoking status:*

All of the included articles enrolled participants who were in good general health. Seven of the experiments (I, II, III a+b, V, IX and XI) excluded smokers. Three (VI, VII and VIII) asked the subjects to abstain from smoking prior to the study. Two experiments (IV and X) did not describe the inclusion or exclusion criteria concerning smoking habits.

- *Periodontal status:*

Periodontal health was an inclusion criterion for the majority of the experiments. Experiment #IV did not report on the gingival/periodontal health of the participants. Only two experiments (III a+b) implemented specific eligibility criteria for the subjects' periodontal status [mild to moderate chronic gingivitis patients with gingival indices of 1–2 for each individual tooth, Löe & Silness, (43)].

- *Oral malodor:*

In total, seven experiments selected participants based on specific criteria for bad breath. Experiment X had the same inclusion criteria as both experiments III a+b [≥80 ppb (parts per billion) of VSCs in morning breath]. Experiment VII selected only oral malodor patients with an organoleptic score >1 using an arbitrary 0–5 scale and a VSC level of >170 ppb as determined with a portable sulphur compound detector (Halimeter®; Interscan Co., Chatsworth, CA, USA). In addition, based on an arbitrary 0–5 scale, experiment XI included subjects with scores ≥4, and experiment IX included subjects with scores ≥2. The baseline VSC levels of the included participants for experiment IX were recorded with the OralChroma®, which specifically measures H_2S. In experiment IX, the inclusion criterion for H_2S was >50 ppb. Experiments # I, VII, VIII and XI state that they used a mean score measured by two judges. The other two studies that used organoleptic measurement only used one judge (# VI and IX). None of the studies explicitly described how judges were calibrated for the organoleptic assessment. The VSC levels in study IV were measured using a gas chromatograph, and only participants with a VSC level ≥300 ppb were included. The other five experiments were not explicit about patient selection with regard to the level of oral malodor (I, II, V, VI and VIII).

Characteristics of the intervention and hygiene instructions

All but one experiment (XI) required subjects to fast prior to the assessments. Moreover, three (VII, VIII and IX) instructed the subjects to abstain from eating strong-smelling

Table 1. **(a) An overview of the selected short-term (<3 weeks) study articles. (b) An overview of selected longer-term study (≥3 weeks) articles.**

Study #/Author (year) Title	Design and evaluation period, risk of bias‡	# of subjects at baseline (end), gender, age, subject characteristics	Groups (products)	Instruction on use ml s^{-1} Per day	Authors' conclusion
(a) An overview of the selected short-term (<3 weeks) study articles					
I. Shinada *et al.*, (2010) (44)	RCT Crossover Double-blind 7 days Low	15 (15) volunteers ♀: 0 ♂: 15 Mean age, 22.9 Range, 19–38 Medically healthy, non-smokers	ClO_2 *MW* (Fresh®, Pine Medical Co., Tokyo, Japan) Placebo *MW*	10 ml 30 s 2× daily	A mouthwash that contained ClO_2 improved morning bad breath as measured by OM and reduced the concentrations of H_2S, CH_3SH and $(CH_3)_2S$ that were measured by gas chromatography in healthy subjects. Moreover, the use of ClO_2 mouthwash over a 7-day period was effective in reducing tongue coating; however, future studies are needed to examine the more long-term effects of mouthwash in halitosis patients and in broader population samples
II. Peruzzo *et al.*, (2007) (10)	RCT Crossover Double-blind 4 days Low	14 (14) dental students ♀: 6 ♂: 8 Mean age, ? Range, 18–25 Medically + periodontologically healthy	0.1% ClO_2 *MW* (SaudBucal®, Saudbucal® Project, São Paulo, Brazil) Placebo *MW*	15 ml 60 s Gargle last 10 s 3× daily	A mouthrinse that contained chlorine dioxide seems to maintain VSCs at lower levels in morning breath when compared to a placebo mouthrinse
III. a+b Rassameemasmaung *et al.*, (2007) (42)	RCT Parallel Double-blind 2 weeks Low	60 (60) students ♀: 48 ♂: 12 Mean age, 26.15 Range, 17–37 Mild to moderate chronic gingivitis, ≥ 80 ppb VSC in morning breath, medically healthy	Herbal *MW* (prepared by the Faculty of Pharmacy, Mahidol University, Bangkok, Thailand.) Placebo *MW*	15 ml 60 s 2× daily OP: No (a) & Yes (b) (two experiments)	Herbal mouthwash that contained the pericarp extract of Garcinia mangostana may be used as an adjunct in treating oral malodor
IV. Boyd *et al.*, (2007) (75)	RCT Crossover Blinding? 1 week High	14 (14) volunteers ♀: ? ♂: ? Mean age, ? Range, ? Subjects with baseline VSC levels ≥ 300 ppb were enrolled Medically healthy	0.05% CPC + 0.025% NaF *MW* (Colgate® Plax, Colgate-Palmolive Company, New York, NY) Placebo *MW*	? ml 30-s rinse + 30-s gargle + 20-s rinse with water 2× daily	The overnight reduction in VSCs was significantly better than baseline levels as well as a placebo rinse

Table 1. (*Continued*)

Study #/Author (year) Title	Design and evaluation period, risk of bias‡	# of subjects at baseline (end), gender, age, subject characteristics	Groups (products)	Instruction on use ml s^{-1} Per day	Authors' conclusion
V. Carvalho *et al.*, (2004) (26)	RCT Crossover Double-blind 4 days Low	12 (12) dental students ♀: 5 ♂: 7 Mean age, ? Range, 19–23 Medically + periodontologically healthy	0.05% CPC *MW* (Cepacol® Gessy Lever Co., Unilever Division, Vinhedo, São Paulo, Brazil) 0.03% Tri+ 0.2% Cp *MW* (Plax® Colgate-Palmolive, Division of Kolynos do Brasil Ltda, Osasco, São Paulo, Brazil) 0.064% Thm, 0.09% Euc + 0.042% Men *MW* (Listerine® Procter & Gamble Laboratories, Surrey, UK) 0.12% CHX *MW* (Periogard® Colgate-Palmolive, Division of Kolynos do Brasil Ltda, Osasco, São Paulo, Brazil) Positive C 0.2% CHX *MW* (Proderma Laboratories Piracicaba, São Paulo, Brazil) Negative C (hydro-alcoholic)	15 ml 60 s 2× daily	Mouthrinses can reduce morning bad breath, and this reduction is not exclusively attributable to the reduction in supragingival plaque formation
VI. Quirynen *et al.*, (2003) (76)	RCT Crossover Double-blind 7 days Moderate	8 (?) medical students ♀: 5 ♂: 3 Mean age, 20 Range, ? Volunteer medical students Periodontologically healthy, no systemic antibiotics for the past 4 months	0.2% CHX + Alc *MW* (Corsodyl®, SmithKline Beecham, Genval, Belgium) 0.05% CHX + 0.05% CPC +0.14% Zn-la *MW* (Halita®, Dentaid, S.A., Barcelona, Spain) 125 ppm AmF + 125 ppm SnF *MW* (Meridol® mouthrinse, GABA international A.G., Münchenstein, Switzerland) Placebo *MW*	10 ml 60 s Gargle last 10 s 2× daily	The strong correlation between odour production from incubated saliva and clinical assessments of morning breath odour suggests that the saliva incubation test may be used as an indirect method to measure oral hygiene products
VII. Roldan *et al.*, (2003) (28) + Winkel *et al.*, (2003) (41)	RCT Parallel Double-blind 2 weeks Low	40 (40) halitosis patients ♀: 19 ♂: 21 Mean age, 43.8 Range, 21–84 Halitosis of oral origin, organoleptic score >1, VSC values >170 ppb, tongue-coating index >4 Medically + periodontologically healthy	0.05% CHX + 0.05% CPC +0.14% Zn-la *MW* (Halita®, Dentaid, S.L., Barcelona, Spain) Placebo *MW*	15 ml 60-s gargling 2× daily	The tested mouthrinse was effective for the treatment of oral halitosis

Table 1. (*Continued*)

Study #/Author (year) Title	Design and evaluation period, risk of bias‡	# of subjects at baseline (end), gender, age, subject characteristics	Groups (products)	Instruction on use ml s^{-1} Per day	Authors' conclusion
VIII. Quirynen *et al.*, (2002) (59)	RCT Crossover Double-blind 7 days Moderate	16 (16) students ♀: 10 ♂: 6 Mean age, 20.5 Range, ? Periodontologically healthy, no antibiotics for the last 6 months	0.2% CHX + Alc *MW* (Corsodyl®, SmithKline Beecham, Genval, Belgium) 0.05% CHX + 0.05% CPC + 0.14% Zn-la *MW* (Halita®, Dentaid, S.A., Barcelona, Spain) 125 ppm AmF + 125 ppm SnF *MW* (Meridol® mouthrinse, GABA international, A.G., Münchenstein, Switzerland) Placebo *MW*	10 ml 60 s Gargle last 10 s 2× daily	Morning halitosis can be successfully reduced by using CHX-Alc, CHX-CPC-Zn or AmF/SnF2^{Mr} mouthrinses twice a day
(b) An overview of selected longer-term study (≥3 weeks) articles					
IX. Wigger-Alberti *et al.*, (2009) (48)	RCT Parallel Double-blind 3 weeks High	? (174) volunteers ♀: 144 ♂: 32 Mean age, 43.1 Range, ? Medically healthy + periodontologically healthy	250 ppm AmF/SnF + 0.2% Zn-la *MW* 0.05% CHX + 0.05% CPC + 0.14% Zn-la *MW* (Halita®, Dentaid, S.A., Barcelona, Spain) 0.12% CHX *MW* (Perio-Aid® Maintenance, Dentaid, Barcelona, Spain) Control *TW*	15 ml 60 s 2× daily No gargling	The newly developed mouthrinse product was able to significantly reduce oral malodorin patients with increased OR or VSC values
X. Codipilly *et al.*, (2004) (60)	RCT Parallel Double-blind 4 weeks Moderate	50 (48) subjects ♀: 28 ◇ ♂: 20 ◇ Mean age, 40.2 ◇ Range, 21–69 ◇ ≥ 80 ppb VSC levels in the morning breath Medically + periodontologically healthy	ZnC + $NaClO_2$ *MW* (TriOral® triumph pharmaceuticals Inc., St. Louis, MO, USA) ZnC *MW* (BreathRx® Discus Dental, Inc., Los Angeles, CA, USA) Placebo *MW*	20 ml 30 s 2× daily	Zinc chloride plus sodium chlorite mouthrinse (TriOral) is more effective in reducing oral malodor than a zinc chloride-alone mouthrinse. Zinc chloride plus sodium chlorite is also even more effective than the no zinc chloride/no sodium chlorite mouthrinse control
XI. Borden *et al.*, (2002) (74)	RCT Parallel Double-blind 4 weeks Low	95 (84) volunteers ♀: 66 ♂: 29 Mean age, ? Range, 19–65 Medically + periodontologically healthy Organoleptic score ≥4	0.064% Thm, 0.09% Euc + 0.042% Men *MW* (Listerine® Antiseptic, Pfizer, Inc., Morris Plains, NJ, USA) 0.075% CPC *MW* (BreathRx® Dicus Dental, Inc., Culver City, CA, USA) ClO_2 + Zn-ac *MW* (Oxygene®, Oxyfresh Worldwide, Inc., Spokane, WA, USA) Placebo *MW*	? ml ? s 2× daily	The four mouthrinses reduced oral malodor within 4 h of a single usage. CPC was the most effective, and the placebo was the least effective. The daily use of EO, CD/Zn and placebo rinses for up to 4 weeks did not reduce oral malodor from week 0 baseline values, and the effects on oral malodor were comparable among these three mouthrinses. CPC was the only mouthrinse that reduced oral malodor from baseline values after 2 and 4 weeks of daily use

‡For details on methodological quality scores, see Appendix S2.

Alc, Alcohol; AmF, Amine fluoride; CHX, Chlorhexidine; ClO_2, Chlorine dioxide; Cp, Copolymer; CPC, Cetyl pyridinum chloride; Euc, Eucaliptol; Men, Menthol; MW, Mouthwash; NaF, Sodium fluoride; $NaClO_2$, Sodium chlorine dioxide; OM, Organoleptic measurement; OP, Oral prophylaxes; RCT, Randomized controlled trials; SnF, Stannous fluoride; TC, Tongue coating; Thm, Thymol; Tri, Triclosan; TW, Tap water; VSC, Volatile sulphur compounds; Zn-ac, Zinc acetate; Zn-la, Zinc lactate; ZnC, Zinc chloride; ZnO, Zinc oxide.

?: Data unknown. ◇: Data calculated by the authors of this review.

foods, such as onions, garlic and spices, for 48 h before the measurements. Five experiments (I, V, VII, VIII and IX) also required subjects to abstain from alcohol for at least 12 h prior to the assessment. For the majority of the experiments (except III a+b, IV, X and XI), subjects were asked to refrain from using scented cosmetic products, such as shampoo, body lotion, perfume and deodorant. Only one study (XI) did not report on toothbrushing in the morning prior to assessment. All other experiments asked subjects to refrain from any oral hygiene overnight before the measurements.

Most studies allowed subjects to continue their usual oral hygiene habits. Four experiments provided a standardized toothpaste (IV, VII, IX and XI), whereas two other studies provided a standardized toothbrush (IX and XI).

Four experiments specifically instructed the subjects to rinse with the mouthwash after brushing (III a+b, IX and X). For two experiments, the order of rinsing and gargling was unclear. The procedure for the participants in experiment IV involved rinsing followed by gargling. Subjects in experiment VII had to avoid rinsing and were only allowed to gargle. The amount of mouthwash used and duration for each rinsing are summarized in Table 1.

Industry funding

Five experiments were supported by a non-commercial grant (I, II, III a+b and V). Industry funding was donated by the following companies: GABA International AG, Therwil, Switzerland (VIII and IX); Dentaid SL, Barcelona, Spain (VII); Pine Medical Company, Tokyo, Japan (I); Triumph Pharmaceuticals Inc., St. Louis, MO, USA (X); and Discus Dental Inc., Culver City, CA, USA (XI). Additionally, SaudBucal® provided study products for experiment II, and the same company scientifically supported study V. Two articles were written by authors who were commercially related to the Colgate-Palmolive Company Technology Center, Piscataway, NJ, USA (IV), and Discus Dental, Inc. (XI).

Study quality

The quality assessment items, including external, internal, and statistical validities for longer- and short-term studies, are presented in Appendix S2. Based on a summary of these criteria, the estimated potential risk of bias is low for seven of twelve experiments (I, II, III a+b, V, VII and XI), moderate for three experiments (VI, VIII and X) and high for two experiments (IV and IX).

Study outcomes between groups

Short-term studies

Four short-term studies evaluated the effect of CHX mouthrinses (Table 2). In total, these studies represented seven interventions with CHX alone or in combination with additional ingredients, such as cetyl pyridinum chloride (CPC) and zinc (Zn). Of these experiments, six interventions showed a significant effect on VSC scores in comparison with the controls. In total, three of five interventions confirmed this finding. These studies also evaluated the effect on organoleptic scores. Only one experiment (VII) evaluated the effect of CHX on tongue coating, and no difference was found between the experimental and placebo groups. In total, two experiments evaluated a CPC-contained mouthwash, and one of these experiments showed a beneficial effect with respect to VSC scores when compared with the controls. Two experiments evaluated an amine-stannous-fluoride mouthwash. The results were inconclusive for these experiments because one study showed a positive effect on both VSC and organoleptic scores, whereas the other study found no significant difference for either parameter when compared to the placebo group. Two experiments assessed ClO_2 and found a significant effect on VSC scores. Only one of these experiments provided relevant information with respect to tongue coating and found no difference between the treatment and control groups. One experiment from Thailand evaluated the effect of an herbal extract (*garcina mangostana*) and observed a positive effect on VSC scores. Another experiment assessed the effect of an essential oil mouthwash on VSC scores and found a significant reduction in the scores. One last experiment compared a triclosan product to controls and found a significant reduction in VSC scores.

Longer-term studies

A 3-week-long study (IX) evaluated two CHX mouthwash concentrations, 0.12% and 0.05%, and an amine-stannous fluoride mouthwash. This study showed that both interventions were significantly more effective than the control rinse with respect to VSC and organoleptic scores.

Two other longer-term experiments (X and XI) evaluated CPC, $(Na)ClO_2$ and ZnCl. These products were more effective against oral malodor than the placebo in terms of VSC and/or organoleptic scores (Table 2b). Little evidence is available concerning the effect of mouthwashes on tongue coating. Only two short-term experiments evaluated this parameter and found no difference.

Evidence profile

The GRADE system was used to rate the quality of the evidence that was obtained from the included studies (40). For the various active ingredients (see Box 1), only studies <3 weeks in duration supplied sufficient support for this assessment with the exception of ClO_2. Of the studies that were ≥3 weeks in duration, only one experiment supported the efficacy of the various active ingredients. However, the evidence from this experiment could not be qualified. Based on the available data, the quality of evidence was rated moderate for the CHX+CPC+Zn combined product and low or very low for CHX, CPC, AmF and ClO_2.

Table 2 **(a) A summary of the significant differences in efficacy of mouthrinses with active ingredients in comparison with a control/placebo for the included short-term studies. (b) A summary of the significant differences in efficacy of mouthrinses with active ingredients in comparison with a control/placebo for the included longer-term studies.**

Study #	Subjects	Mouthwash ingredient	Organoleptic score	VSC	Tongue coating	Control/ placebo
Short-term studies <3 weeks duration						
V	MBB	0.12% CHX	☐	+	☐	Control
V	MBB	0.2% CHX	☐	+	☐	Control
VI	MBB	0.2% CHX + Alc	0	0	☐	Placebo
VIII	MBB	0.2% CHX + Alc	+	+	☐	Placebo
VI	MBB	0.05% CHX + 0.05% CPC + 0.14% Zn-la	0	+	☐	Placebo
VII	OM	0.05% CHX + 0.05% CPC + 0.14% Zn-la	+	+	0	Placebo
VIII	MBB	0.05% CHX + 0.05% CPC + 0.14% Zn-la	+	+	☐	Placebo
IV	OM	0.05% CPC + 0.025% NaF	☐	0	☐	Placebo
V	MBB	0.05% CPC	☐	+	☐	Control
VI	MBB	350 ppm AmF + 125 ppm SnF	0	0	☐	Placebo
VIII	MBB	350 ppm AmF + 125 ppm SnF	+	+	☐	Placebo
II	MBB	0.1% ClO_2	☐	+	☐	Placebo
I	MBB	0.1% ClO_2	?	+	0	Control
IIIa	MBB	Herbal	☐	+	☐	Placebo
IIIb	MBB	Herbal + OP	☐	+	☐	Placebo + OP
V	MBB	0.064% Thm + 0.09% Euc + 0.042% Men	☐	+	☐	Control
V	MBB	0.03% Tri + 0.2% Cp	☐	+	☐	Control
Longer-term studies ≥3 weeks duration						
IX	?	0.12% CHX	+	+	☐	Control
IX	?	0.05% CHX + 0.05% CPC + Zn-la	+	+	☐	Control
XI	OM	0.075% CPC	+	?	☐	Placebo
IX	?	250 ppm AmF/SnF + 0.2% Zn-la	+	+	☐	Control
XI	OM	0.064% Thm + 0.09% Euc + 0.042% Men	0	?	☐	Placebo
XI	OM	ClO_2 + Zn-ac	0	?	☐	Placebo
X	MBB	$NaClO_2$ + ZnC	☐	+	☐	Placebo
X	MBB	ZnC	☐	+	☐	Placebo

OM, Oral malodor (halitosis); MBB, Morning bad breath; morning breath measurement.
+ = significant difference in favour of intervention.
0 = no significance.
? = inconclusive data, which do not allow drawing conclusions for statistical significance.
☐ = no data available.
For ingredient abbreviations, see the legend to Table 1.

Discussion

The mouth is home to hundreds of bacterial species that produce several fetid substances during protein degradation (44) and result in oral malodor. Normal breath is sweet smelling and has an aroma that is similar to the scent of blooming chestnuts. Restoring this aroma is a sought-after goal for millions who suffer from oral malodor, which is a problem that creates a barrier between the subjects and their friends, family and co-workers (45). Commercially available products, such as mints, toothpastes, mouthrinses, sprays and chewing gums, attempt to control oral malodor with pleasant flavours and fragrances (39). However, these products do not treat the causes of oral malodor. Mints and chewing gum without active ingredients have been found to have no significant effect on tongue dorsum malodor three hours after use (39, 46, 47).

A range of over-the-counter mouthrinses for controlling mouth odour has been available for some time (9). These products claim efficacy not only by masking malodor but also by reducing and preventing the overgrowth of opportunistic pathogens. The optimal mouthrinses for oral malodor are thought to be antiseptic agents with proven, long-lasting efficacy in reducing organoleptic scores and VSC levels. Furthermore, these products should have little or no side effects because it may be necessary to use them over longer periods of time (48). A significant number of studies have investigated this issue over the last 30 years. Therefore, it was somewhat surprising to find so few randomized controlled trials comparing the effectiveness of mouthrinses (9).

Although this review provides some evidence for the comparative effectiveness of different mouthrinses, the results must be weighed carefully against the methods that were used to assess their outcome (9). The three main methods of analysing oral malodor include organoleptic evaluation, gas chromatography (GC) and sulphide monitoring. Gas chromatography is performed with an apparatus that is equipped with a flame photometric detector. It is specific for the detection of many gases that emanate from the mouth. Gas chromatography, which is the most reliable, objective and reproducible method

for measuring oral malodor, is considered to be the gold standard. Gas chromatography can be specific for VSCs, which are the primary cause of oral malodor. Moreover, GC can quantitatively analyse the concentrations of the three primary malodor-causing substances: (H_2S), (CH_3SH) and (($(CH_3)_2S$) (9, 49–52). Sulphide monitors analyse for the total sulphur content of a subject's mouth air and are not specific for VSCs (8, 25, 51, 53). For example, the Halimeter® has a high sensitivity for hydrogen sulphide but low sensitivity for methyl mercaptan, which is a significant contributor to oral malodor that is caused by periodontal disease. The most practical procedure for evaluating a patient's level of oral malodor in a dentist's office is the organoleptic evaluation (8, 25). Organoleptic scoring is a sensory test based on the examiner's perception of a subject's oral malodor (8). Direct assessment of breath malodor is a reflection of what the breath recipient actually encounters and is most relevant to the halitosis sufferer (9). The human nose is extremely sensitive because it is capable of detecting very low concentrations of odourous volatiles. Consequently, the development of comparable instrumentation has been a challenge (12). A recent publication assessed the relationship between organoleptic scores and the Halimeter® or gas chromatography, where the correlations between the three methods of breath measurement were high, which implies that all methods are equally capable of assessing oral malodor and that any method on its own might also be sufficient (54).

Table 2a demonstrates that most data represent VSC scores for studies that were <3 weeks in duration. In studies that also provide organoleptic scores, most data agree with the VSC outcomes. For studies ≥3 weeks in duration, both organoleptic scores and VSC readings are common measures in the included studies and study outcomes agree with one another. The studies assessed VSC levels primarily with the Halimeter® (6/8 studies that were <3 weeks in duration and 2/3 studies that were ≥3 weeks in duration).

The ADA has established Acceptance Program Guidelines that apply to products that have been designed for the management of oral malodor of a non-systemic origin (37, 38). These products are active chemical agents as well as mechanical products. Only one study that has been included in this review satisfies all of the clinical ADA guidelines (XI). Depending on the claims being made, oral malodor measurements should be taken at a minimum of two appropriate time points after a baseline measurement during a 3-week test period. Additional appropriate measurements should be obtained based on the product claims. For example, an overnight product should be assessed on day 2 at the minimum. Consequently, the present review only included studies that required mouthrinse evaluation for a period of more than 1 day, and these studies were grouped by those that assessed subjects for <3 weeks and those that assessed subjects for ≥3 weeks. Of these two time frames, the latter is recommended by the ADA. For each of the various active ingredients, at most, only one paper was available to support their longer-term (≥3 weeks) effect with the exception of ClO_2.

Table 3 shows an estimated evidence profile of the included studies and active ingredients. Only studies <3 weeks in duration provided supporting data for CHX, CHX+CPC+Zn, CPC and AmF. Of these products, the combination of CHX, CPC and Zn had the best evidence profile, although the quality of the evidence was still moderate. Chlorhexidine is considered to be the gold standard for oral antiseptics [for a review, see Addy *et al.* (55)]. Unfortunately, CHX, as with most active antiseptics, has some disadvantages, including tooth and tongue staining, bad taste and reduced taste sensation (56, 57). The replacement of alcohol in a CHX formulation with CPC did not change the antibacterial activity but did reduce some of the side effects, especially the bad taste (58). This is not surprising because CPC, which is a cationic quaternary ammonium compound, is known to have antibacterial activity (59). Zinc seems to be an

Table 3. **Evidence profile for the impact of mouthwashes with active ingredients in comparison with placebo or control on oral malodor (from the included short- and longer-term studies of this systematic review)**

	CHX (short)	CHX+CPC+Zn (short)	CPC (short)	AmF (short)	ClO_2 (short and long)
Risk of bias	Low to moderate	Low to moderate	Low to high	Low to moderate	Low
Consistency	Consistent	Consistent	Inconsistent	Inconsistent	Consistent
Directness	Not generalizable	Indirect	Not generalizable	Not generalizable	Not generalizable
Precision	Available data are insufficient to determine precision	Available data are insufficient to determine precision	Imprecise	Available data are insufficient to determine precision	Too little data to support estimate
Publication bias	Possible	Possible	Uncertain	Possible	Uncertain
Quality of evidence	Low	Moderate	Very low	Very low	Low

The grade for VSC scores was based on ingredients that were reported by more than one study.
No attempt was made to grade the body of evidence involving organoleptic measurements or tongue coating because the included studies did not consistently assess these parameters.
For ingredient abbreviations, see legend to Table 1.

effective and safe metal at concentrations of 1% (39). Although the antimicrobial effects of zinc on plaque bacteria have been reported, the zinc ion inhibition of VSC production has been largely attributed to its affinity for sulphur (60).

Morning bad breath is the most common complaint and is attributed to physiological causes (23). The primary cause of morning oral odour is oral dryness, which occurs during sleep when salivary flow and oxygen availability are at their lowest. This environment promotes the anaerobic formation of VSCs (23). Rather than testing real oral malodor patients, subjects with morning bad breath have been accepted as alternative models for testing treatment strategies for bad breath. Recruitment of true halitosis patients is difficult and challenging to standardize (59). Morning breath odour tends to be transient in nature in contrast to persistent oral malodor; however, both malodor conditions appear to primarily result from the above-mentioned excess quantities of sulphur-containing gases of bacterial origin (59, 61, 62). Therefore, therapies that reduce morning bad breath may also be beneficial for the treatment of malodor of oral origins (59). The present review included three studies that recruited true oral malodor patients as their participants (IV, VII and XI). The other studies either did not describe the baseline malodor status of their participants (IX) or used subjects with morning breath (I, II, III, V, VI, VIII and X).

The tongue surface is the main strong odour–forming site in the mouth (6). It is believed that the bacterial mass that is located on the posterior dorsum of the tongue is the principal origin for malodorous compounds (20, 41, 63). This part of the tongue is difficult to reach and exhibits a number of oval cryptolymphatic units that roughen the region. The anterior part of the tongue is even rougher because of the high number of papillae. These innumerable depressions in the tongue surface are ideal niches for bacterial adhesion and growth (64). Moreover, the removal of tongue coating does reduce VSCs (11, 20, 65–67). Quirynen *et al.* (18) observed that a reduction in tongue coating was not associated with clear changes in the microbial load. This result seems to indicate that the beneficial effect of tongue cleaning in halitosis patients is caused by eliminating the substratum that is used by the anaerobic species rather than by removing the bacteria. The role of the tongue coating in oral malodor production probably resides in the composition of the tongue coating rather than the thickness or extent of the coating (28, 41). In the present review, no studies were included that combined mechanical tongue cleaning with mouthrinses. Only two studies evaluated the tongue coating, and these studies showed no beneficial effect of the mouthrinse with active ingredients over the placebo control for this parameter.

There were only three studies that met the ADA study requirements of ≥3 weeks of duration. For each active ingredient, only one study was available. In combination with the data that were obtained in studies that were <3 weeks in duration, it appears that all mouthrinses that claim an effect on oral malodor provide some benefit; however, the quality of the evidence is 'very low' to 'moderate' and is primarily based on studies <3 weeks in duration. The best available evidence was found for the combination CHX+CPC+Zn mouthrinse. In the absence of high-quality evidence for studies of sufficient duration, all products that are claimed to be effective must endure the scrutiny of the marketplace, and only those of merit should survive. This is not an ideal situation for such a socially relevant complaint, and it deserves more attention from the dental scientific community. Further studies should supply dental professionals with adequate data for evidence-based decision-making.

Limitations

- A potential limitation of this study may be the issue of the estimated risk of bias. Allocation concealment is the one aspect of bias protection that has been shown to significantly impact bias (68). Trials with unclear methods (e.g. for allocation concealment) should be assessed as having a moderate risk of bias at best. When the articles that were included in this review are assessed in the light of this parameter, there is only one article with a low risk of bias (I). For the appraisal of study quality (Appendix S2), allocation concealment was not considered in the risk of bias estimate. Although the authors recognize that this is an important issue, they are also aware that reporting on allocation concealment in the dental literature has not been a critical item until recently. Therefore, including this item would result in an overestimation of the risk of bias and would reflect upon study reporting rather than study conduct. However, future study researchers should provide information on this subject, which is also an item of the CONSORT statement (69, 70).
- Publication bias: Included papers of the present review primarily reported on the beneficial effects of the active ingredients. Preferential publication of a positive direction and statistical significance of result may represent a publication bias.
- Language bias: The use of studies that were exclusively written in the English language may be another limitation. It is conceivable that authors are more likely to report in an international, English-language journal if the results are positive, whereas negative findings may be published in a local journal. While the potential impact of studies that have been published in languages other than English in a meta-analysis may be minimal, it is difficult to predict in which cases this exclusion may bias a systematic review (71).
- Some papers used female subjects as their panellists. It has been reported that the menstrual cycle (72) has an effect on VSC scores. This might have an undefined impact on the outcome of the included studies.
- Examiner/patient blinding is another practical limitation. Because the CHX experimental groups will become evident after some time as a result of staining, examiner and patient blinding are not particularly relevant in such a treatment group. This is a limitation that cannot be overcome.
- Tangerman and Winkel (73) have suggested that the hardware of the Oral Chroma meets all the needs for becoming the apparatus of choice in the field of halitosis. However, the software needs a major revision. None of the included studies provide any comment in this respect. The effect of this software problem can therefore not be substantiated.

Conclusion

In this review, nearly all of the mouthwashes with active ingredients were shown to have a beneficial effect with respect to oral malodor in both short- and longer-term studies. This may be indicative of a publication bias. This may represent a publication bias. The most evidence was available for CHX mouthwashes, and combination treatment with CPC and Zn provided the best evidence profile. Little data with respect to tongue coating were available, and none of the studies showed a beneficial effect in regard to this parameter.

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Conflict of interest

The authors declare that they have no conflict of interest.

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Supporting information

Additional supporting information may be found in the online version of this article:

Appendix S1. An overview of the excluded studies.

Appendix S2. Methodological quality scores of the included short-term (<3 weeks) and long-term (≥3 weeks) studies.

Appendix S3. (a–c) An overview of the selected studies for organoleptic measurement, VSC measurement and tongue-coating evaluation within groups.

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*All included long- and short-term studies for this review.